REMARKS

1. Status of the Claims

Claims 1, 2, 6, 7, 48-60, and 62-67 are pending. Based on the body of the Office Action, claims 1, 2, 6, 7, 48-60, and 62-67 stand rejected. Applicants note that the rejection status of claims 1, 2, 6, and 7 is not addressed in the Office Action Summary.

Applicants have amended claims 1, 2, 6, and 7. Support for the amendments can be found, for example, at least in the claims originally as filed as well as for example on page 20, lines 3-10. Applicants have cancelled claim 52. Applicants have amended the claims and cancelled claim 52 without disclaimer of or prejudice to the subject matter cancelled by way of the amendment. Applicants reserve the right to file a continuation or divisional application on the cancelled subject matter.

2. Status of the Drawings

The drawings filed on February 3, 2003, are indicated again as acceptable.

3. Status of the Information Disclosure Statement

The Office indicates that the Information Disclosure Statement filed August 9, 2006 is acknowledged. However, the Office has not returned an initialed copy of the PTO-1449 with the Office Action mailed March 27, 2007.

Additionally, upon review of the application, Applicants call to the Examiner's attention that initialed copies of PTO-1449 forms for Information Disclosure Statements filed October 10, 2000, June 8, 2001, and July 14, 2004 remain outstanding. Applicants respectfully request initialed copies of these three previously submitted 1449 forms as well as that submitted August 9, 2006, with the Office's next communication.

4. Acknowledgement of Continued Examination Under 37 C.F.R. § 1.114

Acknowledgement of the Request for Continued Examination filed August 9, 2006, is noted.

5. Claim Objections

Claim 6 is objected to because of an informality of a duplicative "and". Applicants have amended the claim to remove the duplicate word, thereby mooting the rejection. Applicants request withdrawal of the objection.

6. Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 2, 6, 7, 4-60, and 62-67 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office states that "reduces" can be interpreted to have more than one meaning, e.g., it can mean to reduce the amount of the lipid or be reducing by chemical or electrical means.

Applicants disagree with the Office's interpretation in view of what the application as a whole teaches. "Reducing" would not have been contemplated by the skilled artisan to include reducing by chemical or electrical means given the teachings of the specification. However, in order to advance prosecution, Applicants have amended claims 1 and 6 (and thereby all the dependent claims) to no longer recite "reducing" but instead "decreasing." *Ipsis verbis* support for decreasing is located, for example, at page 20 of the specification. Accordingly, the rejection is mooted, and should be withdrawn and the claims allowed.

7. Rejection of the Claims Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 1, 2, 6, 7, 48-60, and 62-67 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The claims are rejected for a purported introduction of new matter for the use of the word "reduce" in claims 1 and 6.

Applicants traverse the Office's position that "reduce" is new matter. While the word is not explicitly used in the specification with regard to decreasing the level of lipid, other synonyms are used. Applicants remind the Office that *ipsis verbis* support in any specification is not the legal standard. *See, e.g., Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1578 (Fed. Cir. 1996). When an artisan of ordinary skill reads the claims in view of the specification and what it conveys as a whole, the skilled artisan would have concluded

that "reduced" means decreased amounts of a lipid. For example, decreasing lipid levels is discussed on page 20, lines 3-10, especially line 7. However, in an effort to advance prosecution, Applicants have amended claims 1 and 6 to recite the term "decrease" thereby mooting the rejection. Withdrawal of the rejection and allowance of the claims is respectfully requested.

Claims 2 and 7 are also separately rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Recitation of "mRNA" in claims 2 and 7 lacked description, because mRNA would not be expected to bind to a nucleic acid or polypeptide of HBM/Zmax1. The term has been deleted from the claims, thereby mooting the rejection. Applicants request allowance of the claims.

Claims 1, 2, 6, 7, 48-60, and 62-67 appear to stand rejected on page 6 of the Office Action under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. However, there is no argumentation as to what aspect of the claims fails to comply with the requirement. Accordingly, there is no *prima facie* case of lack of written description evinced. Applicants address the paragraph in order to be responsive to all aspects of the rejection.

On page 6, third paragraph, of the Office Action, the Office asserts that claims 1, 2, 48-52, 54, 56, and 65 as lacking written description. The Office alleges that the claims encompass "a HBM or Zmax1" nucleic acid or polypeptide, and that the scope of sequences could be large and also have functions that are different from the disclosed sequences. Applicants have amended claim 1 to recite specific sequences, which have been admitted to have sufficient written description. Accordingly, Applicants respectfully request withdrawal of the rejection, and allowance of the claims.

Claim 52 is also separately rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Without acquiescing to the merits of the rejection, Applicants have cancelled the claim.

In view of the above argumentation and amendments, Applicants respectfully request withdrawal of the rejection and allowance of claims 1, 2, 6, 7, 48-60, and 62-67.

8. Rejection of the Claims Under 35 U.S.C. §§ 101 and 112, First Paragraph, Combined

Claims 1, 2, 6, 7, 48-60, and 62-67 stand rejected under 35 U.S.C. § 101, because the claimed invention allegedly is not supported by either a substantial and specific utility or well established utility. The Office admits on page 11 that identifying molecules associated with diseases [associated with high lipid levels] is credible, and therefore Applicants have asserted a "credible utility." *See* Office Action, page 11, ¶1. However, the Office alleges that the claims lack a "substantial AND specific utility." *Id.*, ¶2. The Office asserts that the claims lack specific utility, because the HBM/Zmax1 molecules can be substituted with "any molecule," and the method still practiced. Office Action, page 13, ¶3. The Office then asserts that the "substantial utility" is lacking because additional experimentation would be required in order to determine that the identified molecules which bind to HBM and reduce a lipid, actually are involved in reducing the lipid. Office Action, page 14, ¶3.

Applicants traverse the rejection and maintain that the Patent Office has failed to successfully challenge the presumption of utility asserted in the specification. The Patent Office has the initial burden to challenge an asserted utility. *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995). To overcome the presumption of truth held by Applicants' asserted utility, the Office must establish that ***it is more likely than not*** that one of ordinary skill in the art would doubt the truth of the statement of utility. In fact, no statement for utility even has to be specifically stated. It must merely be apparent to one of ordinary skill in the art. *In re Folkers*, 344 F.2d 970, 145 U.S.P.Q. 390 (C.C.P.A. 1965). Thus, the Office must provide sufficient evidence to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art. *See, e.g.* 60 F.R. 36263 (July 14, 1995). The Office certainly has not proven that the claimed invention and associated specific utility would have been considered false at the time. Applicants have supplied post filing published articles which further show the correlation between Zmax1 and lipids.

Specific Utility. The Office asserts that one component to consider in factoring specific and substantial utility is the complexity of lipid regulation. The Office asserts, for example on page 12 of the Office Action, that regulation of lipid levels is "a very complex process that involves not one single factor, but many different factors including diet as well

as the function of many different genes." Applicants turn to *In re Brana*, as a helpful analogy to the instant case. In *Brana*, the Office had argued that there was insufficient utility of the claimed compounds to treat *cancer* and that a significant amount of experimentation was required to use the compounds as anti-tumor agents. Cancer, in its many forms, is complex and like lipids, can involve many pathways. Yet, the Court held that treating cancer with chemical compounds did not suggest an inherently unbelievable undertaking or involve implausible scientific principles. *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995). Likewise, the assertion that lipid modulation is complex fails to merit the weight the Office accords it.

Here, Applicants claim a screening method to screen for reagents that bind to Zmax1, or its polymorphic variant, HBM. The candidate reagents are screened for ability to bind to the nucleic acid or polypeptide. The candidate reagent is then also tested to determine whether they decrease a lipid level. Applicants assert in numerous places in the specification that Zmax1 and HBM are involved in lipid regulation. A disclosure that identifies a particular biological activity of a compound and explains how that activity can be utilized in a therapeutic application provides a specific activity. *See, e.g.* 60 F.R. 36263 (July 14, 1995). Likewise, Applicants' use in a screening assay provides a specific utility.

Applicants provided evidence in the specification that (1) Zmax1, currently referred to in the literature as LRP5, is a member of the LDL receptor family; and (2) alignment of LRP5 and what was known about it at the time, was known. The relationship of the LRP5 in the LDL receptor family is illustrated in Figure 3 of Sheryl Brown et al., "Isolation and Characterization of LRP6, a Novel Member of the Low Density Lipoprotein Receptor Gene Family," *Biochem. & Biophys. Res. Comm.* 248: 879-888 (1998) provided below:

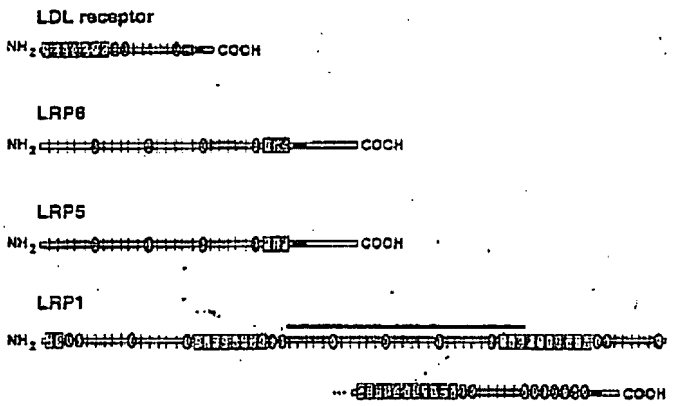

FIG. 3. Motif organization of the LDL receptor, LRP6, LRP5, and LRP1. The LDLR repeats are represented by the light gray boxes, and the EGF repeats are represented by the gray ovals. The YWTD spacer motifs are indicated by the vertical lines. The putative transmembrane domains are represented by the small black boxes. The O-linked glycosylation domain present in the LDL receptor is indicated as a checkered box.

(3) Contrary to the Office's allegation on page 23, ¶1, Applicants teach the specific function of HBM or Zmax1. The asserted utility is that Zmax1/HBM is involved in lipid regulation. This is a specific asserted utility and not a general biological activity. This is asserted throughout the specification.

(4) The fact that at the time of filing LDL-receptors were known to be involved in functions other than lipid regulation is not dispositive of Applicants' asserted specific utility. Applicants showed an altered lipid profile and ApoE binding to Zmax1. Given that the LDL receptors were also associated with lipid regulation, the observation of the family expressing the polymorphic variant (HBM) having an enhanced lipid profile (lower triglyceride levels and generally lower VLDL levels), and the structural similarity between LRP1, LRP5 (Zmax1) and LRP6 shown above would *not* have led the skilled artisan at the time to doubt the asserted specific utility. The reference by Zabaglia regarding HDL levels in post-menopausic women does not, as asserted on page 20, render the data observed as to VLDL and triglyceride levels invalid, or otherwise make false the gene's or protein's involvement in lipid regulation. Applicants have even provided post-filing data in the form of references by others to demonstrate that others have also accepted that Zmax1 (LRP5) action in lipid regulation (references previously of record).

(5) The Office asserts that Applicants fail to demonstrate that Zmax1/HBM is *directly* involved in lipid regulation. Applicants assert that *direct* or *indirect* involvement is not a statutory requirement for evincing utility. Like *Brana*, having anti-tumor activity was sufficient for purposes of a specific utility even though cancer is complex. A detailed

explanation of how an invention works is not a statutory requirement of §101, let alone proof of "direct" activity over "indirect" activity in a pathway.

(6) The Office asserts on page 13 that HBM/Zmax1 could be substituted with "any molecule" that regulate lipids. They could not. The claims turn on screening reagents that bind to HBM/Zmax1 nucleic acids or proteins and further decrease a lipid.

(7) On page 12 of the Office Action, the Office relies on *Knapp v. Anderson*, 177 U.S.P.Q. 688 (C.C.P.A. 1973). *Knapp* is an interference case wherein the Court determined on appeal from the Board whether the subject matter of a "count" had been reduced to practice. Reduction to practice for purposes of utility of an interference count is not a requirement. The reliance on *Knapp* is misplaced.

Therefore, for at least the above reasons as well as the information and argumentation previously made of record, claims 1, 2, 6, 7, 48-60 and 62-67 have a specific utility.

Substantial utility. The Office further asserts that claims 1, 2, 6, 7, 48-60 and 62-67 lack a substantial utility. Substantial utility is a real world use. The Patent Office indicated during a Customer Partnership Meeting that an assay for screening compounds is a real world use. This is further substantiated in MPEP at §2107.01 "Substantial Utility". Screening assays are not a throw away utility such as a transgenic mouse being used as snake food. As discussed above, additional experimentation to determine whether HBM and Zmax1 are involved in lipid regulation would not have been necessary at the time, because the skilled artisan would have not doubted Applicants asserted utility in view of the teachings in the specification and what was known in the art at the time. Therefore, the claims possess a substantial utility.

For these reasons, a *prima facie* case of lack of utility has not been adduced. The combined rejection under 35 U.S.C. §§ 101 and 112, first paragraph, should be withdrawn.

9. Rejection of the Claims Under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 6, 7, 48-60, and 61-67 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

Applicants traverse the Office assertion that "the nature of the invention is a biological assay to identify molecules that reduce a lipid wherein said molecules exert their effect either directly or indirectly through Zmax1 or HBM." Office Action, page 16. The

Office then asserts on page 17 that "there is no disclosure in the specification which indicates either HBM or Zmax1 is a functional LDL receptor that is directly involved in lipid regulation." As a consequence, the Office concludes that further experimentation would be required to practice the claims.

Applicants traverse the rejection. Applicants point out that the candidate reagents screened must bind to a Zmax1 or HBM polypeptide or nucleic acid, therefore, it would appear the claims require a "direct action." The complexity of lipid regulation does not itself alter the binding reaction" or make this aspect of the claims lacking in enabling disclosure, as pointed out by the Court in *Brana* with regard to cancer.

The Office argues that "there is no disclosure in the specification which indicates either HBM or Zmax1 is functional LDL receptor directly involved in lipid regulation." What the Office means by "direct" versus "indirect" involvement in lipid regulation is unclear. Additionally, there is no statutory requirement that involvement be "direct" for the purpose of claiming a screening assay. As discussed in Section 8 *supra*, Applicants provide evidence in the specification as well as post-filing evidence demonstrating that Zmax1 and its polymorphic variant HBM is involved in lipid regulation. The point here is whether one requires further experimentation to make and use the invention. Applicants provide the gene and the polypeptide. Applicants discuss that triglycerides and VLDL are decreased in the HBM patient population. Models to assess lipid levels *in vivo* and *in vitro* existed in the art at the time as previously argued. Thus, no further experimentation is necessary to make and use the claims. The Office appears to support its argument on the requirement that to be patentable, one must explain "how" something operates. Screening assays have been used for a long time, wherein full elucidation of the scientific principle was not known or needed for the purposes of the screen. In fact, how or why an invention works is not required for patentability. *See Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989)

Therefore, for all these reasons, the claims, as amended, are enabled by the specification for the purpose of making and using the method to screen for reagents. Applicants respectfully request withdrawal of the rejection.

10. Office's Response To Applicants' Arguments

On pages 21-24, the Office responded to Applicants' Arguments. Applicants have discussed these points above.

CONCLUSION

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0573. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is respectfully requested and the fee should also be charged to our Deposit Account. If any issues remain outstanding, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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